Oxaliplatin and Gemcitabine – germ cell

Indication
Palliative treatment for relapsed metastatic seminoma, non seminoma or combined tumours.

ICD-10 codes
Codes pre-fixed with C38, C48, C56, C62, C63, C75.3.

Regimen details

Day	Drug	Dose	Route
1 and 8	Gemcitabine	1000mg/m^2	IV infusion
1	Oxaliplatin	130 mg/m^2	IV infusion

Cycle frequency
21 days

Number of cycles
Usual maximum 6 cycles. Consultant decision to give further cycles.

Administration
Administer gemcitabine first. Gemcitabine is administered in 250-500mL sodium chloride 0.9% over 30 minutes.

Oxaliplatin is administered in 250mL glucose 5% over 2 hours.
Oxaliplatin is not compatible with sodium chloride 0.9%. Lines must not be piggybacked or flushed with sodium chloride 0.9% immediately after the infusion.

Patients should be observed closely for platinum hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of oxaliplatin. Facilities for the treatment of hypotension and bronchospasm must be available.
If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy: the infusion may be temporarily interrupted and when symptoms improve re-started at a slower infusion rate. Chlorphenamine 10mg IV may be administered.
Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of oxaliplatin and appropriate therapy should be initiated.

Oxaliplatin may cause transient paraesthesia of hands and feet and laryngopharyngeal dysaesthesia (unpleasant sensations in the throat). Onset is during or within hours of infusion and resolves within minutes to a few days. Symptoms are exacerbated by cold, so patients should be advised to take appropriate precautions. This does not require treatment or dose reduction but subsequent infusions should be given over 6 hours.

Pre-medication
Usually none required
Patients who have previously experienced Grade 1 or 2 platinum hypersensitivity should receive the following premedication:
- 45 minutes prior to Oxaliplatin: Dexamethasone 20mg IV
- 30 minutes prior to Oxaliplatin: Chlorphenamine 10mg IV and Ranitidine 50 mg IV

Patients who develop peripheral neuropathy may be considered for calcium gluconate 1g and magnesium sulphate 1g given together in 250mL 5% glucose IV over 20 minutes pre- and post-oxaliplatin infusion. Caution is required in giving this treatment to patients with known hypercalcemia or those receiving therapy with digoxin or thiazide diuretics.

Emetogenicity

This regimen has moderate-high emetic potential.

Additional supportive medication

H_2 antagonist or proton pump inhibitor if required.
Mouthwashes as per local policy.
Oral magnesium supplementation between cycles in addition to the intravenous magnesium administered at the time of chemotherapy if required as per local magnesium replacement guidelines.
Anti-emetics as per local policy.
Consider GCSF as primary prophylaxis from day 9

Extravasation

Oxaliplatin is an exfoliant (Group 4)
Gemcitabine is neutral (Group 1)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days
Calcium	14 days
AFP, HCG, LDH	14 days (repeat on day 1)

Where appropriate offer pre-treatment sperm storage.

Investigations – pre subsequent cycles

Investigation	Validity period
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days
Calcium	7 days
AFP, HCG, LDH	7 days (repeat weekly during treatment)

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Day 1

Investigation	Limit
Neutrophils	≥ 1.5 x 10^9/L*
Platelets	≥ 75 x 10^9/L* (≥ 100 x 10^9/L on day 8)
Calculated CrCl	> 50 ml/min
Bilirubin	≤ 1.5 x ULN

Dose modifications

- **Haematological toxicity**

Day 1:

If neutrophils < 1.5 x 10^9/L or platelets < 75 x 10^9/L delay for 7 days and if recovered resume at full doses. If more than one delay reduce dose of gemcitabine to 75% for all future doses.

If febrile neutropenia (neutrophils < 0.5 x 10^9/L and fever requiring IV antibiotics) – reduce all subsequent doses of gemcitabine to 75% and oxaliplatin to 100mg/m^2.

Day 8:

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Gemcitabine dose**
≥ 1.5	and	≥ 100	100%
1.0 - <1.5	or	50 - 99	75%
< 1.0	or	< 50	Omit day 8 and Re-start next cycle with 75% gemcitabine

- **Renal impairment**

CrCl (mL/min)	**Oxaliplatin dose**
≥ 50	100%
30 – 49	50
< 30	Omit

Gemcitabine

If CrCl < 30mL/min consider dose reduction (consultant decision)

- **Hepatic impairment**

Lack of information available on the use of gemcitabine in patients with hepatic impairment, therefore, used with caution. If bilirubin > 1.5 x ULN, consider reducing dose to 800mg/m^2 (consultant decision).

Oxaliplatin:

Little information available. Probably no dose reduction necessary, consultant decision.

- **Other toxicities**

Oxaliplatin:

If neurological symptoms occur, use the following oxaliplatin dose adjustments:

Toxicity grade	**Oxaliplatin dose**
1	100%
2 (persisting until next cycle)	100mg/m^2
3 (>7 days but resolved before next cycle)	100mg/m^2
3 (persisting until next cycle) or 4	Discontinue

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Nephrotoxicity
Ototoxicity
Neurotoxicity
Laryngopharyngeal dyaesthesia
Infertility
Haemolytic uraemic syndrome*
Interstitial pneumonitis
Secondary malignancy
Long term risk of cardiovascular disease and metabolic syndrome

Osteonecrosis of the hip
*Gemcitabine should be discontinued at the first sign of microangiopathic haemolytic anaemia (such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevated bilbirubin, creatinine, blood urea nitrogen or LDH. Renal failure may not be reversible with discontinuation of therapy, dialysis may be required.

- **Frequently occurring side effects**

Cold sensitivity
Myelosuppression
Constipation, diarrhoea
Stomatitis, mucositis
Alopecia
Nausea and vomiting
Anorexia

- **Other side effects**

Raised transaminase
Electrolyte disturbances
Fatigue
Headache

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

Antibiotics: The renal toxicity of oxaliplatin is potentiated by aminoglycoside antibacterials (e.g. gentamicin) and amphotericin. Aminoglycosides should be avoided. If aminoglycosides are prescribed, close monitoring of renal function and serum antibiotic levels is required.
Avoid all nephrotoxic drugs where possible

Additional comments

Dose related peripheral sensory neuropathy can occur with oxaliplatin. It usually occurs after a cumulative dose of 800mg/m2. It can occur after treatment with oxaliplatin is completed, and is usually reversible, taking approximately 3 – 5 months to recovery.

References

- Summary of Product Characteristics Oxaliplatin (Sanofi) accessed 27 April 2016 via www.medicines.org.uk
- Summary of Product Characteristics Gemcitabine (Hospira) 27 April 2016 via www.medicines.org.uk
- Kollmansberger, C. et al. Combination chemotherapy with gemcitabine plus oxaliplatin in patients with intensively pretreated or refractory germ cell cancer: A study of the German testicular cancer study group (2004). J Clin Oncol 22: 108-14
- Pectasides, D. et al. Gemcitabine and oxaliplatin (GEMOX) in patients with cisplatin-refractory germ cell tumours: a phase II study (2004). Ann Oncol; 15:493-97

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